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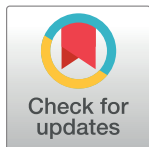
RESEARCH ARTICLE

APOE ϵ 4 and slow wave sleep in older adults

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Data Availability Statement: Data access is legally restricted by the Institutional Review Boards (IRBs) at California Pacific Medical Center and the University of California, San Francisco. Users can access the data through the MrOS Study portal using the following URL: <https://mrosdata.sfcc-cpmc.net/>. Users only have to register for an account and accept the terms of a Data Use Agreement before downloading or exploring clinical data. Additionally, interested researchers may send data access requests to the MrOS Project Director Robin M. Fullman at rfullman@sfcc-cpmc.net or to Christina Kouma of

Abstract

Slow wave (or stage N3) sleep has been linked to a variety of cognitive processes. However, the role of stage N3 in the elderly is debated. The link between stage N3 and episodic memory may be weakened or changed in the older adult population, possibly due to several altered mechanisms impacting the cellular structure of the brain. The bases for the age-related dissociation between stage N3 and cognition are not understood. Since APOE ϵ 4 status is the strongest genetic risk factor for cognitive decline, we assessed whether the ϵ 4 allele is associated with stage N3 sleep. Participants were from the population-based Osteoporotic Fractures in Men (MrOS) cohort with polysomnography and APOE ϵ 4 genotype data ($n = 2,302$, 100% male, mean age 76.6 years). Sleep stages were objectively measured using overnight in-home polysomnography and central electroencephalogram data were used to score stage N3 sleep. Cognitive function was assessed using the Modified Mini Mental State Exam (3MS). The APOE rs429358 single nucleotide polymorphism, which defines the APOE ϵ 4 allele, was genotyped using a custom genotyping array. Total time in stage N3 sleep was significantly higher ($p < 0.0001$) among the 40 MrOS participants carrying two copies of the ϵ 4 allele (62 ± 5.2 minutes) compared with 43 ± 1.5 minutes for carriers of one ϵ 4 allele ($n = 515$) and 40 ± 0.8 minutes for ϵ 4 non-carriers ($n = 1747$). All results were independent of sleep efficiency, number of sleep cycles, and apnea hypopnea index. These findings support an association between APOE ϵ 4 genotype and sleep stage N3 in the elderly. Increased total stage N3 duration among ϵ 4/ ϵ 4 carriers does not appear to reflect compensation for prior cognitive decline and may reflect overactive downscaling of

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synapses during sleep. If confirmed, these results might in part explain the high risk of age-related cognitive decline and AD among APOE $\epsilon 4/\epsilon 4$ carriers.

Introduction

Sleep disturbances and specific sleep disorders increase with advancing age [1–6] and elevate the risk for a variety of diseases and conditions [7–22] including cognitive impairment [23–33]. Recent research indicates that sleep may specifically impact the cellular structure of the brain, including the ability of the brain to clear toxic metabolites that accumulate with normal neuronal function [34]. This includes beta-amyloid [34], which accumulates in apolipoprotein E (*APOE*) $\epsilon 4$ genotype carriers [35] and contributes to synaptic degeneration and cognitive decline. While the *APOE* $\epsilon 4$ allele is a well-established risk factor for Alzheimer's disease (AD) and age-related cognitive decline [36–42] as well as a risk factor for sleep apnea [43–51], *APOE* $\epsilon 4$ has not been assessed in relation to sleep stage distributions. To explore the hypothesis that *APOE* $\epsilon 4$ influences sleep architecture, we examined the effect of the *APOE* $\epsilon 4$ allele on sleep stage distribution measured in a large, population-based cohort of elderly participants with a focus on stage N3, which represents the synchronization of cortical EEG activity and has been implicated in memory formation in young populations [52–57]. Given the high risk of cognitive decline and AD among *APOE* $\epsilon 4$ carriers, identifying a genetic link with stage N3 sleep could advance the development of new approaches for interventions to slow the decline in cognitive function among $\epsilon 4$ allele carriers and that may also benefit the health and well-being of the elderly.

Materials and methods

Participants

Data were collected from participants of the Osteoporotic Fractures in Men (MrOS) Study which included participants who were at least 65 years old and excluded participants who required assistance with ambulation or had undergone bilateral hip replacement. In the MrOS study, 5994 older men were recruited from six geographical areas (Birmingham, AL; the Monongahela Valley near Pittsburgh, PA; Minnaeapolis, MN; Palo Alto, CA; San Diego, CA; and Portland, OR) between 2000 and 2002. The MrOS Sleep Study, an ancillary study of the parent MrOS cohort, was conducted between December 2003 and March 2005 and recruited 3135 MrOS participants (68%) for a comprehensive sleep assessment and assessment of circadian gene polymorphisms. Of the 2,859 men who did not participate in this ancillary study, 344 died before the sleep visit, 36 had already stopped participating in the study, 332 were not invited because recruitment goals had already been met, 150 were not eligible and 1,997 refused. Among the participants of the MrOS Sleep Study, 2480 self-identified white men who had DNA extracted for genetic studies. Details regarding the studies have been published previously [58,59]. All data were collected with written informed consent as approved by the institutional review boards of the clinical sites (University of Alabama at Birmingham; University of Minnesota; University of Pittsburgh; Stanford University; Oregon Health & Science University, and University of California, San Diego) and the coordinating center (University of California, San Francisco). The Outcomes of Sleep Disorders in Older Men Study (MrOS Sleep Study) [60], an ancillary study of the parent MrOS Study, enrolled 3,135 participants from 2003–2005. Of the 3135 enrolled participants, 2911 had usable PSG data and, of these, 2745 (94%) with evaluable sleep staging data. The Modified Mini Mental State Exam [61,62] (3MS),

an expanded 100 point version of the original MMSE, was administered in MrOS at the baseline and sleep exams (~3 years) [63]. The Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS) questionnaires were administered at the sleep exam.

Polysomnography

In-home, single night sleep studies using unattended polysomnography (PSG, Safiro, Compumedics, Inc., Melbourne, Australia) were performed as previously described [64,65]. The recording montage consisted of C₃/A₂ and C₄/A₁ electroencephalograms, bilateral electrocuculograms, a bipolar submental electromyogram, thoracic and abdominal respiratory inductance plethysmography, airflow (using nasal-oral thermocouple and nasal pressure cannula), finger pulse oximetry, electrocardiogram, body position (mercury switch sensor), and bilateral leg movements (piezoelectric sensors). Trained certified staff members performed home visits for setup of the sleep study units. After sensors were placed and calibrated, signal quality and impedance were checked, and sensors were repositioned as needed to improve signal quality, replacing electrodes if impedances were elevated, using approaches similar to those in the Sleep Health Heart Study [66]. After studies were downloaded, they were transferred to the Case Western Reserve University Reading Center (Cleveland, OH) for centralized scoring of sleep stages and sleep disorders by a trained technician using standard criteria [67,68]. Sleep was staged in 30-sec scoring epochs and electroencephalogram data were used to score stage N3 using the criteria of Rechtschaffen and Kales [67]. Total time (minutes) and percent time [$100 \times (\text{Number of minutes scored as stage 3-4}) / (\text{total sleep time})$] in stage N3 were calculated for these analyses. The apnea hypopnea index (AHI) was calculated as the total number of apneas and hypopneas per hour of sleep (4% desaturation) [69]. Sleep cycles were defined using a modified version of the rules detailed by Feinberg and Floyd [70]. A cycle was defined as a period of at least 15 minutes of NREM sleep starting with stage N2 or N3 and terminated by the end of a period of REM sleep lasting at least 5 minutes for all cycles except cycle 1, or a period of wake or stage N1 lasting 15 minutes or longer. Two epochs of REM sleep separated by no more than 15 minutes of NREM sleep or wake were merged into a single REM period. Average absolute spectral power density in $\log_{10}(\mu V^2/\text{Hz})$ was calculated for each sleep cycle for the following bands: Slow oscillation: 0.25–1 Hz, Delta: 1.25–4 Hz, Theta: 4.25–8 Hz, Alpha: 8.25–12 Hz, Sigma: 12.25–15 Hz, and Beta: 15.25–20 Hz. There was excellent inter-scanner reliability for the key sleep parameters, including stage N3 (ICCs >0.92). Several additional sleep parameters were scored, including: wake after sleep onset time and sleep efficiency.

APOE genotyping

The *APOE* rs429358 SNP, which defines the *APOE*ε4 allele, was genotyped using a custom Illumina Golden Gate assay (Illumina, San Diego, CA, USA) that included 529 SNPs as previously described [71]. All individuals in this study are of European ancestry and are unrelated. Of 2,745 MrOS participants with PSG, 2,302 were genotyped for the rs429358 C/T alleles, which define *APOE*ε4 status by the presence of the C allele. All participants in this analysis are of European ancestry.

Statistical analyses

Associations between *APOE*ε4 status and sleep staging were based on 2,302 MrOS participants with both PSG and rs429358 genotype data. All PSG and cognition measures were treated as continuous variables in analyses examining both additive and dominant genetic models to examine *APOE*ε4 associations for total time and percent time spent in stage N3. All regression

models were adjusted for age and clinic site with additional models including measures of sleep duration (TST), quality (WASO time and sleep efficiency) and AHI. Cognitive function change (~3 years) from the visit prior to sleep assessment was calculated and used to stratify stage N3-cognition analyses into high and low decline groups. All analyses were analyzed using SAS version 9.4 (SAS Institute Inc, Cary, NC).

Results

Differences in age, cognition, sleep performance and stage N3 across three *APOEε4* categories are shown in Table 1. Total stage N3 time was significantly higher among 40 MrOS participants carrying two copies of the ε4 allele (62±5.2 minutes) compared with 43±1.5 minutes for carriers of one ε4 allele (n = 515) and 40±0.8 minutes for ε4 non-carriers (n = 1747). The *APOEε4* association with stage N3 time (p = 0.0002) was not altered by adjustment for 3MS (p = 0.0001). We examined the *APOEε4*-stage N3 association among MrOS participants who had experienced either ≥2 point decline or <2 point decline (based on median change) from the previous 3MS assessment to the 3MS measured at the sleep visit. Total stage N3 time was significantly higher among participants carrying two copies of the ε4 allele when compared to the other genotype categories in both the group with ≥2 point 3MS decline (p<0.0001) and the group with <2 point decline (p = 0.0002) and the test for interaction between *APOE* allele and 3MS decline was not significant (p = 0.21). In addition, the *APOEε4* association with 3MS

Table 1. Characteristics of MrOS participants with PSG sleep staging and *APOE* genotyping.

	<i>APOEε4</i> alleles				
	0	1	2	p-value ^a	p-value ^b
n (%)	1747 (75.8)	515 (22.5)	40 (1.7)		
	mean (SE)	mean (SE)	mean (SE)		
Age, y	76.6 (0.1)	76.5 (0.2)	75.6 (0.9)	0.48	0.13
3MS (0 to 100)*	93.4 (0.1)	92.4 (0.2)	90.2 (0.8)	< .0001	0.003
Change 3MS* ^c	-1.01 (0.1)	-1.47 (0.2)	-3.34 (0.7)	0.0025	0.0026
Time in stage N3 (min)*	40 (0.8)	43 (1.5)	62 (5.2)	< .0001	< .0001
Change 3MS ≥ -2	41 (1.0)	42 (1.8)	61 (7.4)	0.03	0.008
Change 3MS < -2	38 (1.4)	45 (2.5)	64 (7.5)	0.0005	0.002
Time in REM (min)*	70 (0.7)	68 (1.2)	65 (4.5)	0.21	0.13
Time in stage N1 (min)*	24 (0.3)	24 (0.6)	22 (2.1)	0.68	0.48
Sleep efficiency (%)*	76 (0.3)	76 (0.5)	81 (1.9)	0.05	0.01
Wake after sleep onset (min)	115 (1.6)	116 (2.8)	86 (10)	0.02	0.005
Apnea hypopnea index (4% desat)*	13 (0.3)	12 (0.6)	14 (2.1)	0.57	0.56
Number of sleep cycles*	4.7 (0.03)	4.6 (0.1)	4.6 (0.2)	0.50	0.97
Spectral power density- SOsc (log ₁₀ (uV ² /Hz))* ^d	1.9 (0.01)	1.9 (0.02)	2.0 (0.6)	0.15	0.06
Arousal index	24 (0.3)	23 (0.5)	24 (1.9)	0.10	0.93
PSQI*	5.6 (0.1)	5.5 (0.1)	5.3 (0.5)	0.69	0.55
ESS*	6.1 (0.1)	6.1 (0.2)	5.7 (0.6)	0.76	0.47
Hypnotics, n	38	10	0		

* Adjusted for age

^a Linear p-value across three genotypes

^b P-value comparing carriers of two ε4 alleles to all others

^c Baseline to sleep visit ~ 3 years.

^d Spectral power density of the C3-A2 EEG in the slow oscillation (0.25–1 Hz) band for the final sleep cycle.

PSQI = Pittsburgh Sleep Quality Index; ESS = Epworth Sleepiness Scale

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($p < 0.0001$) was not altered by adjustment for stage N3 time ($p < 0.0001$) and the test for interaction between APOE $\epsilon 4$ and stage N3 time in the association with 3MS was statistically significant ($p = 0.006$). The APOE $\epsilon 4/\epsilon 4$ genotype was associated with higher sleep efficiency and lower WASO but not the PSQI or ESS assessments. Spectral power density of the C3-A2 EEG in the slow oscillation (0.25–1 Hz) band was calculated for the final sleep cycle and did not differ among APOE alleles (Table 1). The total number of sleep cycles did not differ among APOE alleles (Table 1). The APOE associations with total stage N3 time did not change after additional adjustment for sleep efficiency ($\epsilon 4/\epsilon 4 = 59 \pm 5.2$ minutes, $p = 0.0003$), wake after sleep onset ($\epsilon 4/\epsilon 4 = 60 \pm 5.2$ minutes, $p = 0.0002$), number of sleep cycles ($\epsilon 4/\epsilon 4 = 64 \pm 5.6$ minutes, $p = 0.0001$), or AHI ($\epsilon 4/\epsilon 4 = 62 \pm 5.1$ minutes, $p < 0.0001$).

Discussion

In the present study of >2,300 older men, we confirmed a significant association between APOE $\epsilon 4$ status and lower cognitive function scores and unexpectedly found that APOE $\epsilon 4$ was associated with increased stage N3 duration. Average total stage N3 time was >50% longer among elderly APOE $\epsilon 4/\epsilon 4$ carriers (those who at the highest risk of developing AD and age-related cognitive decline [36–42]) when compared to those with one or no copies of the $\epsilon 4$ allele. While those with the APOE $\epsilon 4/\epsilon 4$ genotype had more stage N3 time, stage N3 was not associated with cognitive decline in MrOS [72], even after adjustment for APOE $\epsilon 4$ status. Consistent with increased stage N3 time among $\epsilon 4/\epsilon 4$ genotype carriers, the APOE $\epsilon 4/\epsilon 4$ genotype was also associated with higher sleep efficiency and decreased WASO, indicating overall less arousability. This finding was unexpected but could reflect a compensatory mechanism wherein the consolidation process is upregulated in reaction to declining cognition. In order to test this possibility we examined the APOE $\epsilon 4$ -stage N3 association among APOE $\epsilon 4/\epsilon 4$ participants who had experienced either high or low ~3-year decline from the previous 3MS assessment. Total stage N3 time did not differ between participants who had experienced either high or low declines suggesting that the longer stage N3 time among $\epsilon 4/\epsilon 4$ carriers is not compensating for prior cognitive decline. It has been suggested that the negative correlations previously observed between stage N3 and subsequent learning in older adults is unlikely due to memory consolidation [73], and might be explained by another function of stage N3 such as synaptic downscaling or pruning [74]. During waking hours, encoding leads to increased synaptic weights which eventually results in the saturation of synaptic networks. The downscaling of certain synapses which takes place during stage N3 likely serves to ensure the maintenance of balanced synaptic input. The negative correlations observed between stage N3 and memory in older adults, however, may reflect an altered balance between daytime encoding and nighttime downscaling wherein older adults engage in less daytime encoding than younger adults [75] but over-downscale if they are still gaining relatively high amounts of stage N3. Thus, an age-related proportional increase in downscaling would presumably become detrimental to memory functioning if synapses that could otherwise help encode new memories are pruned. Such sleep-dependent synaptic downscaling has been observed in *Drosophila* [76,77].

Synaptic plasticity and scaling are crucial mechanisms in memory flexibility and AD onset [73,78,79] with experimental downscaling of AMPA receptors contributing directly to AD pathology [78]. In light of the genetic association data presented herein, it is possible that APOE $\epsilon 4/\epsilon 4$ carriers are experiencing “overactive downscaling” [73]. APOE is produced by the glia in the central nervous system [80], while APOE receptors are expressed on the neuronal cell surface where they mediate lipoprotein uptake and signal transduction [81,82]. It has been proposed that APOE isoforms may differentially accelerate synapse dysfunction and AD

dementia by interfering with APOE receptor-dependent neuromodulation [81]. Of the three APOE isoforms ($\epsilon 2$, $\epsilon 3$, and $\epsilon 4$), APOE $\epsilon 4$ selectively impairs synaptic plasticity and NMDA receptor phosphorylation by Reelin, a modulator of synaptic strength [79]. This selective impairment of APOE receptor signaling by the APOE $\epsilon 4$ isoform leads to a decrease in synaptic responsiveness [79]. The APOE $\epsilon 4$ isoform also reduces glutamate receptor function and synaptic plasticity by selectively impairing APOE receptor recycling in primary neurons [79].

Sleep also impacts the cellular structure of the brain, including the ability of the brain to clear beta-amyloid, contributing to synaptic degeneration and cognitive decline [34]. For example, chronic sleep restriction increases amyloid- β plaque formation in the amyloid precursor protein transgenic mice [34]. Sleep also impacts the ability of the brain to remove potentially toxic biomolecules that accumulate with normal neuronal function, including beta-amyloid [34], which accumulates in APOE $\epsilon 4$ genotype carriers [35]. This "glymphatic system" is strongly stimulated by sleep and is associated with an increase in interstitial volume, possibly by shrinkage of astroglial cells, leading to clearance activity. Clearance during sleep is as much as two-fold faster than during waking hours [34]. Thus, glymphatic dysfunction may play a role in the pathogenesis of neurodegeneration as well as maintenance of cognition. However, it is also possible that accumulation of beta-amyloid and other toxic metabolites may influence synaptic connectivity, and thus influence neurophysiological mechanisms of sleep, altering sleep state distributions [83].

Few studies have examined the role of APOE genotype in both sleep and cognitive performance [84,85]. In a study of 126 cognitively normal adults (30–70 years), chronic daytime somnolence was associated with a distinctive decline in verbal memory among APOE $\epsilon 4/\epsilon 4$ carriers as compared to APOE $\epsilon 4$ heterozygotes and noncarriers [84]. A second study examined how sleep parameters in AD patients change over time as a function of APOE $\epsilon 4$ status [85]. Among forty-four community-dwelling adults with a diagnosis of probable AD there was greater deterioration on sleep parameters (increased WASO time and decreased TST and sleep efficiency) in non-APOE $\epsilon 4$ carriers when compared with positive APOE $\epsilon 4$ carriers [85]. Associations between sleep performance and cognition also differed between APOE $\epsilon 4$ carriers and non-carriers [85]. The APOE $\epsilon 4$ allele has also been identified in studies as a risk factor for sleep apnea, although the associations have not been consistent [43–51]. Despite these previous APOE $\epsilon 4$ -sleep associations, the APOE $\epsilon 4$ -stage N3 results reported herein were independent of objective measures of sleep continuity as well as apnea hypopnea index.

In conclusion, these findings support a role for APOE $\epsilon 4$ genotype in the regulation of stage N3 in the elderly. Despite the established role of stage N3 in executive function [52,53] and memory consolidation [54–57] in younger and middle-aged adults, the link between stage N3 and cognitive function may be weakened or changed in older adult population [73,86–89] (including the MrOS study [72]). The negative correlations between stage N3 and subsequent learning in older adults could involve several altered mechanisms [74,90] (including memory consolidation, synaptic downscaling, or other macromolecular changes during stage N3 [83]). As demonstrated in previous studies, increased stage N3 might predict worse episodic memory consolidation in the elderly [88] and may be detrimental to morning recall [73,91–94]. Similar changes to the sleep–memory link have also been reported for old rodents [95,96] showing that normal hippocampal reactivation is not preserved in older rats and that deep sleep was associated with worse memory performance as measured by performance on the Morris Water Maze task. Further research is needed to confirm the APOE $\epsilon 4$ -stage N3 associations and to identify the mechanism(s) by which APOE $\epsilon 4$ alterations impact sleep architecture. Quantitative EEG analysis will be useful also to elucidate whether APOE influences homeostatic drive and sleep dynamics, and whether such changes associate with cognition. The important strengths of this study are the large number of participants with overnight PSG,

longitudinal cognitive function measures, and *APOE*ε4 genotyping. An additional study strength is the use of a large cohort of older adults who were not selected on the basis of sleep or cognition characteristics. This study, however, was limited to white men and may not be generalizable to other populations or women. If it is confirmed that increased total stage N3 time among *APOE* ε4/ε4 carriers reflects an overactive downscaling of synapses during sleep, these results might in part explain the high risk of AD and age-related cognitive decline among *APOE* ε4/ε4 carriers.

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